Demystifying Caffeine

Is it a blessing or a curse? By Yvette Leung

Ever seen sleep-deprived college students drinking coffee in the wee hours of the morning? Did you ever stop to think if those morning runs to Starbucks actually made you more alert throughout the day? Caffeine is by far the most popular psychoactive stimulant used throughout the world (1). Nearly everyone has fallen victim to caffeinated beverages such as coffee, tea, and soda. In North America alone, 80-90% of adults identify themselves as frequent caffeine users (1). The average person typically consumes 76 mg of caffeine per day, although people in the United States, Canada, and Australia consume more than 230 mg per day (2). While the effects of caffeine are often disputed, many people commonly associate caffeine with alertness, memory, and vigilance in daily tasks (3). However, the side effects of caffeine withdrawal prompt us to question whether or not coffee consumption truly delivers any net advantages to the consumer.

The Role of Caffeine

Caffeine, the most important stimulant found in beverages such as tea and coffee, is a member of a class of drugs known as methylxanthines. Upon entering the body, caffeine binds to adenosine receptors, becoming concentrated in high levels in the brain. Adenosine receptors normally bind to the adenosine molecule, and this process in turn results in the release of GABA, the primary inhibitory neurotransmitter in the brain, which ordinarily slows down bodily processes and induces sleepiness. However, caffeine inhibits adenosine activity by binding to the adenosine receptors instead, thereby preventing the release of GABA and thus the onset of sleep. In addition, caffeine activates certain calcium release channels to cause muscle contractions (4). The dual role of caffeine in stimulating neuronal and muscular activity is responsible for its effect in re-energizing tired individuals.

Although caffeine has been shown to enhance arousal in drowsy individuals, little data exists on the effect of caffeine on alert individuals. An Australian study, however, proved that caffeine indeed has a significant effect on well-rested people. Using a special technique known as infrared reflectance oculography, in which infrared light is shined onto the horizontal axis of the eye and reflected in order to yield data on eye blinking patterns, Natlie Michael’s laboratory, at the Swinburne University of Technology, measured ocular cues such as velocity of eyelid movement and duration of blinks in order to compare the vigilance of well-rested participants with and without caffeine. The oculography results were then examined in conjunction with the Johns Drowsiness Scale (JDS). Higher JDS scores correlate with lower levels of alertness, while lower JDS scores correlate with higher levels of concentration. Scientists discovered that caffeine caused JDS scores to decrease dramatically, indicating that these well-rested participants, too, felt less drowsy after being exposed to
Caffeine Withdrawal

In addition to being a psychostimulant, caffeine also has the ability to induce anxiety. Some psychiatric patients who consume 1000-1500 mg of caffeine daily have begun to be diagnosed with “caffeineism” due to the rise of anxiety disorders exacerbated by high caffeine intake (3). Caffeine-induced anxiety, however, is significantly reduced in habitual caffeine consumers due to increased tolerance. That being said, a recent study at the University of Bristol raises even more basic questions about caffeine use and withdrawal as the team found that caffeine did not increase alertness in non- or low caffeine users. The alertness level of heavy caffeine users who had temporarily been given no caffeine, could only be increased back to the non-caffeine users’ alertness baseline when they were administered caffeine (6). Does this then suggest a contradiction in the traditional use of caffeine as a way to increase alertness? Perhaps the real stimulus for caffeine intake is the debilitating fatigue and headaches caused by caffeine withdrawal (6). Caffeine’s apparent “effect” may very well be an illusion that stems from mitigating the various withdrawal effects of using the drug itself.

These withdrawal syndrome may actually be prompting users to continually consume caffeine. Ten prominent symptoms – headache, fatigue, irritability, decreased energy, reduced alertness, decreased contentedness, depressed mood, difficulty concentrating, drowsiness, and fogginess – have been associated with caffeine withdrawal. Symptoms usually appear around 12-24 hours after consuming caffeine, and severity increases from 20-51 hours. If abstinence continues, symptoms could remain for over a week. In fact, the first documentation of potential symptoms of the syndrome dates back nearly 170 years, demonstrating that impaired behavioral and cognitive performance from caffeine withdrawal is nothing new. More recently documented symptoms of caffeine withdrawal include decreased social interaction, lack of motivation, decreased self-confidence, and decreased motor activity (1).

Genetics of Caffeine Metabolism

The enzyme primarily responsible for metabolizing caffeine is cytochrome P450 1A2 (or CYP1A2), which is found in the liver (9). A study found that the rate of caffeine metabolism is dramatically decreased by a single nucleotide polymorphism from the adenine to cytosine nucleotide at position 163 on the CYP1A2 gene. This point mutation thus genetically predisposes certain individuals to be unable to quickly detoxify high doses of caffeine. In addition, individuals with the cytosine nucleotide at that particular position also suffered from an increased risk of myocardial infarction, commonly known as heart attack (10). In a University of Toronto study, 2,014 heart attack survivors were paired with 2,014 randomly selected healthy individuals. After subjects consumed four cups of coffee per day, scientists discovered that the risk of heart attack was 64% higher in people who had the point mutation. In addition, among those who carried the mutation, drinking four cups or more of coffee per day as compared to drinking one cup or less was 1.5-fold increase in heart attack risk in participants under 59, and with a striking 4-fold increase in heart attack risk in participants under 50 (9).

Genetic variation also plays an important role in caffeine’s effects on the nervous system. As mentioned previously, caffeine primarily binds to adenosine receptors, including the adenosine A2A receptor (ADORA2A). In fact, a specific polymorphism in the gene coding for ADORA2A is associated with decreased caffeine intake. The probability of having the 1083TT genotype in the ADORA2A gene decreases while potential caffeine intake increases. Individuals with the 1083TT genotype therefore have a reduced probability of developing caffeine dependence and tend to exhibit more self-control in limiting caffeine consumption (11).

Effects on Adolescents

Caffeine consumption also affects sleep cycles and focus in adolescents. As adolescents increase caffeine intake, sleep patterns become disrupted and sleep duration is significantly reduced. Caffeine consumption among students, in one survey, was 76% higher on average for those who reported falling asleep during school than for those who did not fall asleep. When paired with the increase in

Figure 1. This caffeine molecule binds to adenosine receptors.
 multitasking among adolescents, the use of caffeine to stay awake might be contributing to a “downward spiral” of sleep deprivation. In this context, it is important to note that less sleep has been associated with various health conditions such as acne, asthma, and even obesity (8).

However, it is easy to see why students continue to drink caffeinated beverages, despite the potentially problematic interferences with the sleep cycle. One Australian study sought to analyze caffeine’s influence on student focus during a 75-minute university lecture. Researchers investigated mood, concentration, and arousal after giving the student experimental group caffeinated beverages. Students in this group described themselves as much more energetic and awake than the students in the control group. The caffeinated beverages also enhanced concentration during the lecture. Low-dose (5-250 mg/kg) caffeine consumption administered 60 minutes before a lecture was shown to improve mood, attention, and dexterity in students. Caffeine may also influence other cognitive functions such as memory. Caffeine stimulates cholinergic neurons - and thus increases information recall from short-term as well as long-term memory. Thus, we can add to our growing store of, at times contradictory, research results on the effects of caffeine that the drug may work to help students process and retain a larger proportion of lecture material (2).

Potential Benefits

Not only do some studies indicate that caffeine really does enhance alertness, but others have also shown that caffeine may have various therapeutic benefits. JW Daly, at the National Institutes of Health, demonstrated that caffeinated beverages might offer protection against Alzheimer’s disease, as well as other neurological ailments. Caffeine has also been investigated as a treatment for ischemic stroke, schizophrenia, and even as a treatment for dependency on other drugs. In addition, caffeine has also been implicated in possibly reducing cancer metastasis. Further research is being conducted on caffeine’s ability to prevent damaged DNA repair during the cell cycle which could contribute to targeting cancer tumor cells (4).

It is clear that more research is needed to determine whether or not caffeine intake in fact produces the benefits that we have, up until now, taken for granted. These exciting new studies indicate that this surprisingly elusive drug might indeed prove beneficial to people suffering from a variety of medical problems - though the net effects of caffeine consumption for the average person remains to be seen. H

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References

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